

3
None of these subjects suffered renal, cardiac, nervous or metabolic disorders (in particular diabetes was excluded). These patients underwent the standard treatment protocol, consisting of once daily hot mud applications for 10 subsequent days. The mud used was a natural clay mixture biologically activated by means of a ripening process based on several months' exposure to running hot spring water at temperatures between 50°C and 80°C. The applied mud packs have an initial average temperature of around 50°C. The mud is applied on the trunk and on the affected part if distal, after which the subject is wrapped in several layers of cotton sheet for at least 30 minutes, during which profuse sweating will typically appear. From all subjects sweat samples were collected, by means of polythene cups applied to the side of the forehead, for at least 10 minutes during the central part of the treatment session. Typically between 1 and 5 ml of transpiration fluid was collected from each subject.

A further series of 19 subjects (average age 40.3 years, range 32 to 52) did not undergo mud baths, but submitted to outside swimming and sunbathing in the same establishments where the thermal therapy was administered. Sweat samples were collected similarly from these subjects after a morning of leisure sunbathing at the hottest time of the day.

Analyses of the single sweat samples were performed as described by Fukumoto et al. (cited hereinabove) and by Hohnadel et al., *Atomic Absorption Spectrometry of Nickel, Copper Zinc, and Lead in Sweat Collected from Healthy Subjects During Sauna Bathing*, *Clinical Chemistry* 19(11): 1288-1292, (1973).

Though lacking an experimental group which engaged in physical exercise, a typical profile for passive heat-induced sweat

C3
C4
emerged from experimental data, as will be summarized as follows:

Please replace the paragraph beginning on page 13, line 16, and ending on page 13, line 22, with the following rewritten paragraph.

C4
In the case of sodium, the essential issue lies in the time/volume rate of sweat production. Indeed, sweat is formed in two steps: production by the secretion coils of primary fluid containing nearly isotonic NaCl concentrations, followed by reabsorption of NaCl in the duct. Ductal reabsorption efficiency being critically influenced by transit time, it is the sweat rate which is the most important factor influencing final NaCl concentration in sweat. Indeed, sweat NaCl is low at the low sweat rate range, increasing to isotonicity with increasing sweat rate.

Please replace the paragraph beginning on page 14, line 26, and ending on page 15, line 3, with the following rewritten paragraph.

C5
Considering the observations on the risk of early skin ageing on repeated exposure to heat, especially if in conjunction with sun or UV exposure, it was further considered appropriate to include, besides a dermatropic element such as zinc, also a significant presence of the main dermoprotective vitamins such as biotin and beta-carotene. Since the main mechanism for cutaneous tissue damage on UV exposure is free radical induction and consequent peroxidation of skin surface lipids, and also considering that the principal hydro-soluble antioxidant ascorbic acid had previously been implicated in heat adaption mechanisms (Strydom et al. *in Effect of ascorbic acid on rate of heat acclimatization*, J. Appl. Physiol. 41(2):

CP
only

202-205, 1976), a significant presence of vitamin C appeared desirable.

Please replace the paragraph beginning on page 15, line 15, and ending on page 15, line 30, with the following rewritten paragraph.

CC

As a preferred alternative, the hydro-soluble glycoside of a natural antioxidant flavonoid, Rutin (quercetin-3-rutinoside) can be included in the composition of the present invention. On intestinal absorption, Rutin is readily metabolized to yield the polyphenol quercetin. The latter compound has recently been reported to be an extremely active free radical trapper, particularly active in protecting Low Density Lipoproteins (LDL) from oxidative damage (deWhalley et al., *Flavonoids Inhibit the Oxidative Modifications of Low Density Lipoproteins by Macrophages* Biochemical Pharmacology 39(11): 1743-1750 1989; Negre-Salvayre and Salvayre, *Quercetin Prevents the Cytotoxicity of Oxidized LDL on Lymphoid Cell Lines*. Free Radical Biology and Medicine 12 101-106 1992; Frankel et al. in *Inhibition of oxidation of human low-density lipoprotein by phenolic substances in red wine*, The Lancet 341: 454-457 1993). Rutin has indeed been reported to potentiate the synergistic antioxidant properties of the two main antioxidant vitamins (C and E) by Negre-Salvayre et al. in *Additional antilipoperoxidant activities of alpha-tocopherol and ascorbic acid on membrane-like system are potentiated by rutin*, Pharmacology 42(S): 262-272, 1991.

Please replace the paragraph beginning on page 16, line 24, and ending on page 16, line 26, with the following rewritten paragraph.

01

On the basis of the above general formula, the following specific compositions, prepared as a beverage, powder for

C7
C8
dispersion in water, or solid forms for oral intake, such as capsules or tablets, are presented:

Please replace the paragraph beginning on page 18, line 20, and ending on page 18, line 27, with the following rewritten paragraph.

C8
The above powder mix can be combined with a suitable support for tablet compression, with good organoleptic properties, such as sorbitol and magnesium stearate. The mass is possibly edulcorated with a known natural sweetener such as xylitol and the total energy content should not exceed 20 kcal in the average daily intake. The product may be flavored with any choice of fruit or other flavors, such as orange, lemon, menthol, eucaplytol, or the like. The compressed tablets (or equivalent solid forms with the same composition) are intended for an average daily intake of between 5 and 10 tablets.

Please replace the paragraph beginning on page 21, line 12, and ending on page 21, line 19, with the following rewritten paragraph.

C9
HOT CLIMATES - In today's modern society the technology of air conditioning has largely reduced the problem of the well known negative influence on human body function of high environmental temperatures. But a consistent chain of conditioned air cannot always be maintained, and a certain level of exposure to outside temperatures is often unavoidable. Less affluent and slower developing economies in geographical areas with hot climates will frequently be exposed to high temperatures, with all the negative effects, for instance when walking outside or traveling.

Please replace the paragraphs beginning on page 22, line 27, and ending on page 23, line 17, with the following rewritten paragraphs.

CI⁰
FEVER - When you run a fever, the body temperature control mechanism is upset due to the presence of an infection or other disturbing factors. The body temperature increases, not due to externally applied heat, but due to internal biological factors. The profuse sweating that is often associated with fever, especially in children, is well known. From a medical point of view a primary objective is the elimination of the infection (by prescribing antibiotics), and checking the fever (by prescribing antipyretics). An additional factor, mostly viewed as being less important from a medical point of view, is the re-establishment of an appropriate electrolyte balance, in the cases where profuse sweating has caused risk of excess electrolyte excretion. It is deemed that sweating due to endogenous heat is similar to sweating induced passively by external heat.

As a matter of fact, it is well known that sports beverages are often prescribed for this purpose. The present invention, while not being a medical treatment of the fever, may better assist to re-establish the balance of electrolytes upset due to sweating induced by endogenous heat.

Apart from the uses specifically discussed above, several other beneficial uses of the invention may be devised. Though the invention was not developed for sports purposes and is not intended to balance electrolyte losses due to heavy physical activity, there are situations of moderate exercise where beneficial effects have been suggested, for example: